MAKING SENSE OF THE PERCHLORATE ACTION LEVEL DEBATE

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In its 2002 external review draft risk assessment of perchlorate (*Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization*), U.S. EPA proposed a revised reference dose (RfD) of 0.00003 mg/kg-day, which translates to a Drinking Water Equivalent Level (DWEL) of 1 ppb. In December 2002 Cal-OEHHA proposed a Public Health Goal (PHG) of 2-6 ppb. U.S. EPA bases its proposed RfD on rat studies, whereas Cal-OEHHA bases its value on a human clinical study by Greer *et al.*, 2002. The proposed RfD and PHG incorporate composite uncertainty factors of 300 and 30, respectively. U.S. EPA's uncertainty factor of 300 is not scientifically supportable and is inconsistent with the best available human data. Cal-OEHHA's uncertainty factor is based on a misreading of those data.

Perchlorate has been used for over 50 years as a medication. This use provides a wealth of information about perchlorate's pharmacodynamics, pharmacokinetics, and possible risk from exposure. Perchlorate's mechanism of action is iodide uptake inhibition (IUI) following a well-known dose-response relationship. IUI is the initial event of a series of reversible biochemical and physiological phenomena that can lead to sustained changes in levels of thyroid hormones--precisely its purpose at therapeutic doses. IUI is not adverse in any respect, but rather a normal and mundane event affected by a host of other routine situations such as eating. Despite this, U.S. EPA and Cal-OEHHA have explicitly or implicitly designated IUI as the "critical event" whose occurrence must be prevented to avoid adverse effects.

Several human studies shed light on the science of perchlorate pharmacology. One particular clinical study has enabled the reliable estimation of a no-effect level (NEL) for IUI (Greer *et al.*, 2002). Consistent results were obtained from another clinical study (Lawrence *et al.*, 2000, 2001). At exposures at or below the NEL, no effects of *any* kind can occur. Thus, adverse effects—however defined—are biochemically infeasible. Setting the RfD or PHG equal to the NEL ensures protection against any conceivable adverse effects for the entire population. Based on Greer *et al*., 2002 the no-observed effect level for IUI is 0.007 mg/kg-day. The true NEL is estimated as 0.0052 mg/kg-day. This translates to a DWEL of 180-220 ppb–about 200 fold greater than the U.S. EPA's proposed RfD and 100-fold greater than the PHG proposed by Cal-OEHHA.

Greer *et al.,* 2002 provides additional insights showing that the rat model does not yield accurate estimates of human health risk. In rats, thyroid hormone levels respond almost immediately to large doses of perchlorate. If rat thyroid response predicts human thyroid response, then similar responses would be observed in humans. However, this did not occur. Subjects given 0.5 mg/kg-day (DWEL ~ 15,000 ppb) for 14 days experienced 67% IUI, but no change in thyroid hormones, TSH, or blood chemistry parameters. It is possible that much larger doses might elicit rapid response such as observed in rats, but larger doses are not relevant to estimating human health risk at environmental exposure levels.

By itself, neither clinical trial provides information about the likely consequences of chronic exposure above 200 ppb. Occupational and epidemiological studies offer useful insights. In the best occupational

study, Lamm *et al.*, 1999 monitored workers at a perchlorate manufacturing facility and found no effects in any parameter measured (including blood chemistry, thyroid hormones, and size of the thyroid gland) at any dose. Workers in the highest dose group received on average 5 years' exposure to approximately 0.5 mg/kg-day (DWEL ~ 15,000 ppb). Greer *et al.*, 2002 predicts that this dose would cause about 70% IUI. Another occupational study by Gibbs *et al.*, 1998 provides supportive information for longer exposure periods, but perchlorate exposure measurement was not as well documented. Crump *et al.*, 2001 observed no changes in thyroid hormone levels or adverse effects in children exposed to natural perchlorate levels up to 110 ppb in drinking water, presumably starting *in utero* through to the age of testing (7 years). Other ecological studies corroborate the absence of effects in humans, including sensitive subpopulations exposed for many years (Li *et al.*, 2000, 2001).

Brechner *et al.,* 2001 and Schwartz 2001 obtained contrary results. Brechner *et al.*, 2000 compared neonates born in two Arizona communities and attributed differences in TSH to perchlorate exposure based on city of mother's residence but without confirmed evidence of perchlorate exposure. Also, this study has been faulted for failing to control for differences in the time of blood draw (which strongly affects neonatal thyroid hormone level measurements) and a number of important confounding factors (Goodman, 2001; Crump and Weiss, 2001). Brechner *et al.,* 2000 asserts that only 6 ppb perchlorate was sufficient to elicit these observed differences, but this exposure level is just 5% of the threshold for IUI.

Similar concerns arise with respect to Schwartz 2001. In addition, the Schwartz study has not been peer reviewed and the author has denied access to data to researchers seeking to reproduce her results.

The NEL, defined at the dose of perchlorate that does not inhibit iodine uptake in the thyroid gland, implicitly protects sensitive subpopulations. Hundreds of years of experience with pharmaceutical agents shows us that a medication cannot exert a therapeutic effect, let alone a side effect, at a dose that has no effect at all via the known mechanism of action. Because IUI is several steps removed from any adverse effect, application of additional safety factors to the NEL for perchlorate (as proposed by U.S. EPA and Cal-OEHHA) is unnecessary. Hypothyroidism, for example, follows after significant and unresponsive changes in thyroid hormone levels, which do not occur unless significant IUI occurs for a sustained period of time. Greer *et al., 2002* and others support this by showing that no changes in thyroid hormones or other blood chemistry parameters occur at perchlorate doses approximately 100 times greater than the NEL. Thus, use of the NOEL/NEL to set a DWEL implicitly incorporates safety factors.

As an indirect means of testing the validity of U.S. EPA and Cal-OEHHA conclusions that ppb-level low exposures to perchlorate might be adverse, we estimated the amount of IUI that should occur from single servings of foods containing other anti-thyroid chemicals. Focusing first on nitrate—which has the identical mechanism of action on the thyroid and is approximately 1/300th as potent as perchlorate per unit of mass--our analyses show that single servings of common nitrate-containing foods would cause tens to hundreds of times as much IUI as the proposed RfD/DWEL or the proposed PHG. Contrary to conventional wisdom, green leafy vegetables contain vastly more nitrate than processed meats and are the greatest "offenders." We estimate one serving of broccoli, celery, or lettuce has the same IUI potential as drinking water with 100 ppb perchlorate. We also estimate that one serving of turnip greens has the same IUI potential as drinking water containing 800 ppb perchlorate. Both estimates are uncertain: the range of scientifically plausible estimates for single servings of broccoli, celery and lettuce is 30 to 4,000 ppb perchlorate equivalent, and the range for turnip greens is 300 to 30,000 ppb.

This comparative exposure assessment shows that IUI is the most mundane of phenomena and that setting the RfD or PHG low enough to prevent it is both scientifically untenable and practically impossible. However, the analysis also shows that the scientific reasoning behind the U.S. EPA and Cal-OEHHA approaches has serious unintended consequences. In particular, carrying forward the estimate that nitrate is 1/300th as potent as perchlorate implies that exposure to 300 ppb nitrate would have the same biochemical effect as 1 ppb perchlorate. This means that the existing Maximum Contaminant Level (MCL) for nitrate (10,000 ppb) is severely under protective and ought to be reduced by at least a factor of 30. Should either U.S. EPA or Cal-OEHHA believe that additional precaution is warranted because of the

vastly greater public exposure to nitrate from multiple sources and pathways, the new nitrate MCL could be well below 300 ppb—perhaps as low as 10 ppb.

In summary, simple principles of pharmacology combined with well-designed human clinical studies and comparative exposure assessment show that perchlorate exposures hundreds of times higher than the proposed RfD or proposed PHG are “safe.” Indeed, a DWEL of 200 ppb for perchlorate is very safe. Given the magnitude of IUI that occurs regularly from a normal healthy diet, it could understate what’s safe by a factor of 10 or more.